EXHIBIT A67

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Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11, 933 Subjects from Sixteen Observational Studies

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Abstract. *Objective: Prior epidemiological studies suggest an association between perineal cosmetic talc use and increased risk of epithelial ovarian cancer. A meta-analysis was performed to evaluate this suspected association. Materials and Methods: Using previously described methods, a protocol was developed for a meta-analysis examining the association between perineal talc use versus non-use and the development of invasive epithelial ovarian cancer. Literature search techniques, study inclusion criteria and statistical procedures were prospectively defined. Data from observational studies were pooled using a general variance based meta-analytic method employing confidence intervals previously described by Greenland. The outcome of interest was a summary relative risk (RRs) reflecting the risk of ovarian cancer development associated with perineal talc use versus non-use. Sensitivity analyses were performed when necessary to explain any observed statistical heterogeneity. Results: Sixteen observational studies meeting protocol specified inclusion criteria were located via a comprehensive literature search. These studies enrolled a total of 11,933 subjects. Analysis for heterogeneity demonstrated that the data were homogenous (p = 0.17) and could be combined in a meta-analysis. Pooling all sixteen studies yielded a RRs of 1.33 (CI = 1.16-1.45), a statistically significant result suggesting a 33% increased risk of ovarian cancer with perineal talc use. Despite this finding, the data showed a lack of a clear dose-response relationship making the RRs of questionable validity. Further sensitivity analyses showed that hospital-based studies showed no relationship between talc use and ovarian cancer risk, i.e. RRs 1.19 (0.99-1.41) versus population-based studies (RRs = 1.38, CI = 1.25-1.52). This suggests that selection bias and/or uncontrolled confounding may result in a spurious positive association between talc use and ovarian cancer risk in population-based studies. Conclusion: The available observational data do not support the existence of a causal relationship between perineal talc exposure and an increased risk of epithelial ovarian cancer. Selection bias and uncontrolled confounding may account for the positive associations seen in prior epidemiological studies.*

Ovarian cancer represents a major cause of mortality and morbidity among women in the United States with over 25,000 cases diagnosed each year. This tumor represents the fourth most common gynecological cancer in the U.S. with over 15,000 deaths annually (1). Overall, ovarian neoplasms account for over 50% of all deaths from tumors of the female genital tract. Ovarian cancer is more common in industrialized countries implicating environmental factors in its etiology.

In 1982, Cramer *et al.* publised the results of a case control study implicating perineal cosmetic talc use in the development of ovarian cancer (2). Subsequently, a number of additional studies have shown small but increased risk among women using cosmetic talcum powder. These statistical associations raise concerns that there may be a cause-effect relationship between perineal talc exposure and ovarian carcinogenesis. This concern is further fuelled by the structural similarity between talc and asbestos, a well-recognized human carcinogen.

Despite the availability of a number of observational studies suggesting an association between perineal talc application and ovarian cancer development, serious questions remain regarding the validity of this finding. These include: (1) the relatively small sample size of most studies limiting statistical power to detect an effect; (2) lack of consistent positive association across studies; (3) absence of demonstrable dose-response relationship; (4) lack of supporting evidence of carcinogenicity from animal or *in vitro* analyses; and (5) the possible presence of uncontrolled confounding producing a spurious positive association

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between talc use and ovarian cancer risk. Due to the above-cited limitations of the available database, a meta-analysis was performed in order to statistically pool all available studies addressing this issue. The results of this analysis should provide a clearer understanding of the association (if any) between perineal talc use and ovarian cancer risk.

Materials and Methods

The methods employed in this analysis have been previously described (3). Briefly, a study protocol was prospectively developed that outlined the purpose and methods of the analysis. Eligibility criteria for the studies were determined prospectively, as were the specific data elements to be extracted from each trial. A plan for data analysis was also formulated as part of the study protocol. A data extraction form was designed for recording relevant data from each published study.

Literature retrieval was performed by previously described methods (8). A MEDLARS search was conducted covering the years January 1966 to January 2001. The CancerLit as well as the EMBASE databases were also fully explored, as was the CD-ROM version of Current Contents. The search included all languages. The search terms used were talc exp ovarian neoplasms. Manual searches of study bibliographies and a review of relevant textbooks supplemented electronic database searches. Bibliographies of relevant review articles were also searched. If a series of papers was published, all data were retrieved from the most recent report.

The initial citations (in the form of abstracts) from this literature search were screened by a physician investigator (oncologist) to exclude those that did not meet protocol specified inclusion criteria. The reasons for rejection included: animal studies, *in vitro* studies, review articles, letters to the editor, abstracts, non-peer reviewed articles and papers dealing with only non-epithelial ovarian tumors. Citations selected from this initial search wre subsequently screened for eligibility using the following criteria:

(1) observational studies enrolling patients with histologically-proven epithelial ovarian tumors excluding tumors of "borderline malignant potential",
(2) studies enrolling adult patients only (*i.e.* 18 years of age or older),
(3) availability of data documenting type of talc exposure (*e.g.* dusting perineum *versus* sanitary napkins *etc.*) and
(4) odds ratio or relative risk with 95% confidence interval for each study or availability of raw data to calculate these parameters.

Citations meeting the above criteria were entered onto an accept log and copies of full papers were obtained. The key data elements extracted from each trial included: number of cases and controls, frequency of perineal talc use, origin of study subjects (*i.e.* hospital *versus* population-based), factors (if any) used to statistically adjust study odds ratios or relative risks, case /control response rates and percentage of subjects reporting talc use. Two researchers performed the data extraction. Differences in data extraction forms were resolved by consensus.

Statistical methods. The data analysis was performed according to meta-analysis procedures previously described by Greenland (4). This meta-analysis method is a general variance-based method employing confidence intervals. Because the variance estimates are based on adjusted measures of effect and on the 95% confidence interval for the adjusted measure, the confidence interval methods do not ignore confounding and are the preferred methodology for observational data. The estimate of the 95% confidence interval from each study is used to estimate the variance of each study's effect measure, *i.e.*

$$\ln RR_s = \frac{\text{sum}\ (w_i \times \ln RR_i)}{\text{sum}\ w_i}$$

where

$$w_i = \frac{1}{\text{variance}\ RR_i}$$

The RR_i are estimates of relative risk and in this instance have been measured as odds ratios. Estimating the variance from the 95% confidence interval is given by,

$$\text{variance}\ RR_i = \left[\frac{\ln (RR_i + RR_l)}{1.96}\right]^2$$

where RR_i is the estimate of the relative risk in the ith study and RR_l is the lower bound of the 95% confidence interval for the study.

A 95% confidence limit for the estimated relative risk is determined as,

$$95\%\ CI = e^{\ln RR_s \pm 1.96 \times \sqrt{\text{variance}_x}}$$

and

$$\text{variance}_x = \frac{1}{\text{sum weight}_i}$$

Prior to estimation of a summary relative risk, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the studies (3). If Q exceeds the upper tail critical value of Chi-square ($p < 0.10$) at k-1 *df* (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies are not measuring an effect of the same size. In this instance, calculation of a pooled estimate of effect (*i.e.* RRs) may be of questionable validity. Study effect sizes may be disaggregated by grouping studies into appropriate categories until Q is not rejected within those categories or regression techniques can be employed. That is, reasons for the observed heterogeneity must be sought. In essence, Q is a diagnostic tool for determining if all the variance in the observed effect sizes is accounted for.

Using the general variance-based meta-analysis method employing confidence intervals proposed by Greenland, Q is calculated as:

$$Q = \text{sum}[\text{weight}_i \times (\ln OR_s - \ln OR_i)^2]$$

Where OR_s and $_i$ are estimated as described above.

Results

The literature search yielded seventeen studies that appeared to meet protocol specifications and full papers were obtained for review (2,5-20). Further review showed that the paper by Hankinson *et al.* (12) used the same data as a subsequent paper by Gertig *et al.* (10) from the same laboratory. Therefore, only reference 12 was included in the meta-analysis. The remaining sixteen papers met protocol specified inclusion criteria.

Table I provides an overview of the included reports. A total of 11,933 subjects were enrolled in fifteen case-control studies and one cohort study. Five of the sixteen reports were hospital-based with the remainder being population-based analyses. The individual odds ratios listed in Table I reflect the odds of exposure in cases and controls with an odds ratio of greater than one suggesting a positive association, *i.e.* an

Table I. *Overview of included studies.*

Author	#cases	#controls	Freq. powder use	OR (95% CI)	Adjustments to OR	Hospital *vs* population
Booth (5)	235	451	never *vs* ever	1.29 (0.92-1.80	-age, SES	H
Chang (6)	450	564	none *vs* any	1.42 (1.08-1.86)	-age, yrs OC use, #full term pregnancies, duration of breast feeding/pregnancy, tubal ligation, hysterectomy, mother or sister with ovarian/breast cancer	P
Chen (7)	112	224	never *vs* ever	3.9 (0.9-10.6)	-education, parity	P
Cook (8)	313	422	none *vs* any	1.5 (1.1-2.0)	-age, education, income, marital status, BMI, OC use, parity	P
Cramer (9)	563	523	never vs any	1.60 (1.18-2.15)	-age, study center, tubal ligation, BMI, parity, OC use, primary relative with breast or ovarian cancer	P
Cramer (2)	215	215	none *vs* any	1.92 (1.27-2.89)	-parity, menopausal status	P
Gertig (10)	307		never *vs* ever	1.05 ((0.84-1.32)	-age, parity, duration of OC use, BMI, tubal ligation, smoking, post menopausal hormone use	P
Godard (11)	170	170	never *vs* ever	2.49 (0.94-6.58)	-age, OC use, parity, tubal ligation hysterectomy, alcohol use	P
Harlow (13)	235	239	never *vs* any	1.5 (1.0-2.1)	-parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	p
Harlow (14)	116	158	none *vs* any	1.1 (0.7-2.1)	-age, parity, OC use	P
Ness (15)	767	1,367	never *vs* ever	1.5 (1.1-2.0)	-age, parity, family Hx ovarian cancer, race, OC use, tubal ligation, hysterectomy, breast feeding	P
Purdie (16)	824	860	never *vs* ever	1.27 (1.04-1.54)	-parity, hysterectomy, tubal ligation, OC use, age, education, BMI, smoking, family Hx cancer	P
Rosenblatt (17)	77	46	never *vs* any	1.0 (0.2-4.0)	-live births	H
Tzonou (18)	189	200	never *vs* any	1.05 (0.28-3.98)	-age, education, weight, age at menarche, menopause, menopausal status, parity, age at first birth, tobacco use, coffee/ETOH use, hair dying	H
Whittemore (19)	188	539	never *vs* ever	1.45 (0.81-2.60)	-parity, OC use	H
Wong (20)	499	755	never *vs* ever	1.0 (0.8-1.3)	-OC use, smoking, parity, family Hx ovarian CA, age at menarche, menopausal status, income, education, geographic location, tubal ligation/hysterectomy	H

OR, odds ratio; CI, 95% confidence interval; OC, oral contraceptive; Hx, history.

increased risk of ovarian cancer. Individual study odds ratios (OR) ranged from 1.0 to 3.9. Nine of the sixteen reports provided some information on dose-response (2, 5, 6, 8, 10, 13, 15, 19, 20). This took the form of either stratifying study subjects on number of perineal talc applications per month or number of years used. As seen in the table, all studies adjusted study odds ratios by various factors although there were differences in the specific adjustments across studies.

Prior to combining all studies to derive a summary estimate of effect (*i.e.* a summary relative risk, RRs) a statistical test for homogeneity was performed, Q). This gave a value of Q equal to 20.29. With 15 degrees of freedom, the p value associated with a Q of this size is 0.17. This indicates that the studies are homogeneous (*i.e.* the studies are measuring

effects of similar magnitudes). Given the lack of statistical heteroeneity, the data were pooled for calculation of a summary relative risk.

Pooling data from all sixteen studies yielded a summary relative risk of 1.33 with a 95% confidence interval of 1.16-1.45, a statistically significant result suggesting a 33% increased risk of developing ovarian cancer with perineal talc exposure *versus* no exposure. Despite the finding of a positive association, demonstration of a dose-response relationship is an important criterion for making causal inferences from epidemiological data. If no relationship exists, a causal link between exposure and disease is questionable. The summary relative risk may in fact be spurious due to bias or uncontrolled confounding.

Seven studies included dose-response data stratified by number of talc application to the perineum per month (Table II). A comparison was made across these studies comparing the lowest recorded exposure category with the highest exposure level. This showed a RRs of 1.83 (1.55-2.15) for the lowest talc exposure group, *i.e.* an 83% increase in ovarian cancer risk *versus* a RRs of 1.21 (1.00-1.45) for the highest talc exposure category (the latter being a non-statistically significant result). These data suggest an inverse relationship between talc exposure and ovarian cancer risk. Unfortunately, only limited data were available in that (1) only a small minority of studies contained dose-response information of any type and (2) substantial differences existed in dose stratification levels among the studies reporting such information. It was therefore not possible to perform more sophisticated modeling of dose-response data (21). Nonetheless, the apparent lack of a dose-response relationship requires further exploration in additional studies. It must be considered that the carcinogenic activity of talc may resemble that of asbestos, although this remains purely speculative. The relationship between asbestos exposure and mesothelioma risk lack a clear dose-response relationship (22). Elucidation of this relationship is complicated by possible differences in biological activity based on fiber type and, possibly more importantly, fiber dimensions. Time since exposure may be a more important parameter in asbestos-related mesothelioma risk than total exposure, although this remains uncertain. How these features of asbestos-related mesothelioma compare to the possible biological activity of cosmetic talc remains questionable.

On further examining Table II, the lowest talc exposure category in the Cramer *et al.* study is "less than 30" applications per month (9). This value is not consistent with the other "low exposure" categories, *i.e.* it is a substantially greater value than seen in any other study. Exposure categories must be roughly similar in order to make valid comparisons across studies. If a sensitivity analysis is performed by dropping this study from the pooled result, a summary relative risk of 1.43 (1.14-1.85) results. Taken together, these data show a lack of a clear dose-response relationship.

Table II. *Dose response data.*

Reference	Years of talc use/OR + 95% CI		#talc application/month /OR + 95% CI	
5		NG	1x	0.7 (0.3-1.8)
			4x	2.0 (1.3-3.4)
			30x	1.3 (0.8-1.9)
6	<30	1.7 (1.09-2.68)	<10	1.84 (1.24-2.73)
	30-40	1.44 (0.96-2.15)	10-25	1.13 (0.74-1.72)
	>40	0.96 (0.54-1.38)	>25	0.95 (0.61-1.49)
8	0-5.5	1.8 (0.9-3.5)		NG
	5.5-13.5	1.6 (0.9-2.9)		NG
	13.5-27	1.2 (0.6-3.4)		NG
	>27	1.8 (0.9-3.4)		NG
9	<20	1.9 (1.2-3.0)	<30	2.2 (1.4-3.6)
	20-30	1.3 (0.8-2.3)	30-39	1.2 (0.8-1.8)
	>30	1.4 (0.9-2.3)	40+	1.6 (0.8-3.1)
10		NG	4-24	0.99 (0.67-1.46)
			>/=30	1.12 (0.82-1.55)
13	<10	1.2 (0.5-2.6)	<5	1.5 (0.8-2.7)
	10-29	1.6 (1.0-2.7)	5-29	1.2 (0.6-2.2)
	>/=30	1.6 (1.0-2.7)	>/=30	1.8 (1.1-3.0)
15	,1	2.0 (1.0-4.0)		NG
	1-4	1.6 (1.1-2.3)		
	5-9	1.2 (0.8-1.9)		
	10+	1.2 (1.0-1.5)		
19	1-9	1.60 (1.00-2.57)	1-20	1.27 (0.82-1.96)
	10+	1.11 (0.74-1.65)	>20	1.45 (0.94-2.22)
20	1-9	0.9 (0.6-1.5)		NG
	10-19	1.4 (0.9-2.2)		
	>/=20	0.9 (0.6-1.2)		

NG, not given.

Fifteen of the included sutdies were of case-control design while reference 10 was a cohort study. Since study design may effect study outcome, a sensitivity analysis was performed by excluding Gertig *et al.* from the analysis and recalculating RRs. This gave a summary relative risk of 1.36, a result almost identical to the initially calculated RRs. Therefore, study design showed little effect on the pooled estimate to effect.

Table I lists the adjusted odds ratios for each included report and the specific adjustments made. As noted earlier, a number of factors are known to influence ovarian cancer risk either positively or negatively, such as parity, oral contraceptive use and infertility. That is, few data are available detailing the demographic and hygienic practices of women using cosmetic talc. Since there are some existing data suggesting a positive association between a high fat diet and increased ovarian cancer risk, a relationship may exist

between weight/body mass index and talc use (10). A sensitivity analysis was performed pooling the six studies that controlled for these parameters (8-10, 13, 16, 18). The summary relative risk obtained was 1.32 with a 95% confidence interval of 1.16-1.49. This analysis showed minimal change in the RRs suggesting that the body mass index / weight does not significantly impact the observed association between talc use and ovarian cancer risk.

Table I shows that five of the included case-control studies were hospital-based (5, 17-20) while the remaining studies were population-based. This fact is important since referral patterns may impact study results. If referral patterns among hospitals in a given city or region differ, the over-referral of exposed cases to one hospital implies an under-referral of cases to the others. Due to "differential referral", a factor may be associated with increased disease risk in one hospital-based study and protective in another. In an individual study, pooling data across hospitals helps eliminate bias from differential admission of cases. Pooling data from several sources in a meta-analysis, as done in the present report, partially accomplishes this. Stratifying the meta-analysis on the source of patients, *i.e.* hospital-*versus* population-derived, demonstrated that the summary relative risk for population-based studies was 1.38 (1.25-1.52) suggesting a 38% increased risk of ovarian cancer among talc users *versus* non-users. Interestingly, pooling all hospital-based studies yielded a RRs of 1.19 (0.99-1.41), a non-statistically significant result indicating a lack of association between talc use and ovarian cancer risk. More frequent talc use among hospital-based control patients *versus* population-derived controls does not explain this finding since the proportion of controls using talc was the same in both groups, *i.e.* 32%. Other factors account for this difference in outcome.

As seen in Table I, the individual study odds ratios are generally in the range of 1.0-2.0. Odds ratios of this magnitude are considered "weak effects". This fact is important in that misclassification of only a small proportion of cases could move an odds ratio from non-statistically significant (*i.e.* OR = 1.0) to significant (*e.g.* 1.2-1.5 *etc.*). One possible explanation of the potentially spurious positive association between talc use and ovarian cancer risk is the existence of a "treatment effect" among cases. Particularly among population-based sudies, a varying proportion of cases will be prevalent rather than incident. Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy and/or surgery. Side-effects from treatment may prompt talc use among some patients. Although many questionnaires may specify talc use prior to diagnosis, patients may not always make the distinction between pre-diagnosis and post-treatment use. Exposure misclassification among "prevalent" cases may cause a spurious finding of an association when none, in fact, exists. No information is available from the published studies regarding types of treatment administered to study subjects. This precluded further exploration of the above hypothesis. If data on time from diagnosis to interview was known, patients could be stratified on this parameter with re-calculation of a summary relative risk. Unfortunately, none of the included studies provided such information.

Overall, the above findings of selection bias due to study design and the clear lack of a dose-response relationship between talc use and ovarian cancer risk brings the previously suggested association into question. The data presented in this meta-analysis do not support a cause-effect relationship between perineal cosmetic talc use and the risk of ovarian cancer development.

Discussion

Talc is a hydrous magnesium silicate with a structural similarity to asbestos fibers. Asbestos is a family of mineral fibers with well-recognized carcinogenic properties. Inhalation of asbestos is associated with an increased risk of lung cancer and mesothelioma, a highly lethal tumor of the chest or abdomen. Mesothelioma may also affect the testis as well as the pericardium. Interestingly, asbestos and talc are often found together in nature with talc deposits contaminated with asbestos fibers (21).

A study of 21 consumer talcum powders labeled as baby powders, facial powders or body powders, obtained from retail stores in New York City between 1971 and 1975 reported that ten contained concentrations of tremolite and anthophyllite asbestos ranging from 0.2 to 14.0 percent (22). Voluntary guidelines were established by the cosmetic industry in 1976 to limit the content of asbestiform fibers in commercial talc preparations, although the magnitude of the risk of ovarian cancer as a result of perineal exposure to talc remains unclear.

In the 1960's it was recognized that female asbestos workers demonstrated an increased risk of ovarian cancer and other intra-abdominal tumors (23). Subsequent retrospective cohort studies of women in various asbestos industries showed a two-fold increase in ovarian cancer with a suggested dose-response relationship. Heller *et al.* (24) showed that substantial amounts of asbestos fibers can be found in ovarian tissue derived from women with fathers or husbands employed in asbestos-related occupations. Women with domestic asbestos exposure were twice as likely to have asbestos fibers in the ovarian tissue as compared with those without such an exposure history. Nonetheless, migration of talc particles from the lower female genital tract to the ovary has not been demonstrated conclusively in other studies (25-27). Asbestos contamination of talc has been identified in the past but current production methods limit or completely eliminate contamination. Asbestos contamination of talc complicates studies that examine ovarian cancer risk among talc workers since it is not possible to determine with certainty the possible independent contribution of talc to cancer risk.

Cramer *et al.* conducted the first study suggesting a link

between cosmetic talcum powder use and ovarian cancer (2). Since that time, a number of additional reports have addressed this question with most showing odds ratios ranging between 1.0 and 2.0. Odds ratios of this magnitude, *i.e.* weak associations, are difficult to interpret. This dogma is based on the fact that the investigator cannot directly manipulate the levels of the exposure of interest or extraneous factors that could affect study findings. Attempts to control for external factors are accomplished by statistical manipulations of collected data. However, this process depends on the accuracy and completeness of data collection. Further, the correct choice and interpretation of both statistical models and statistical findings can also be contentious. For these reasons, odds ratios below 1.5 or 2.0 are often dismissed by epidemiologists as uninterpretable. The danger of this, however, is that an association may be weak but real.

Meta-analysis has been employed in an attempt to overcome the problem of weak associations. If meta-analyses show that the patterns of low relative risk or odds ratios are elevated across all relevant studies in different populations, these weak associations are less likely to be due to study bias or uncontrolled confounding. Nonetheless, even in this instance, if a bias affects all studies in the same manner, an association may be shown although the finding is spurious. If a statistical test for heterogeneity shows effects of different magnitudes across studies, sensitivity analyses can be employed to determine the source of observed variability and thereby identify biases due to study design, case / control selection *etc.* This systematic evaluation of heterogeneity provides valuable information that can contribute to a clearer understanding of possible causal associations and improvement in the design of more definitive studies.

The meta-analysis presented above shows inconsistencies in the available data, *i.e.* clear differences in study findings related to whether studies were hospital-based or population-based. The differences in findings from various research groups may not be entirely due to differences in the source of study subjects *per se* (selection bias), but may be due to the differences in the proportion of incident *versus* prevalent cases across studies. As explained earlier, a "treatment effect" operative among prevalent cases could account for the spurious positive association seen in some studies. Unfortunately, it is not possible to prove this definitively given the existing data-base. Also, the behavioral aspects of talc use are poorly defined. That is, very limited data exist regarding the demographics of hygienic talc use. This information might be useful in providing additional insight into how talc use differs across segments of the female population and how it relates to ovarian cancer risk, if at all.

In addition, the present meta-analysis shows a lack of a clear dose-response relationship between talc exposure and cancer risk. As discussed by Evans (28), demonstration of a dose-response relationship is an important criteria for drawing causal inferences in chronic disease epidemiology. Inability to show increasing incidence with increasing exposure makes a causal association less likely. In fact, the available data seem to indicate an inverse dose-response relationship which is counter-intuitive.

In summary, pooling data from the sixteen available observational studies examining the relationship between perineal use of cosmetic talc and the development of invasive epithelial ovarian cancer failed to show evidence of a causal relationship. Future studies need to examine whether misclassification based on post-treatment talc use leads to a false-positive association between talc use and increased ovarian cancer risk. Additional information on the "demographic profile" of talc users may also provide the basis for improved study design.

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